Probiotics

TRADE NAMES

Bifido Factor (Natren), DDS-Acidophilus (UAS Laboratories), DDS-Junior (UAS Laboratories), DDS-Plus (UAS Laboratories), Digesta Lac (Natren), Healthy Trinity (Natren), Life Start (Natren), Mega Dophilus (Natren), Multiflora-ABF (UAS Laboratories), Probiata (Wakunaga Consumer), Probioplus-DDS (UAS Laboratories).

DESCRIPTION

Probiotics are defined as live microorganisms, including *Lactobacillus* species, *Bifidobacterium* species and yeasts, that may beneficially affect the host upon ingestion by improving the balance of the intestinal microflora. The dietary use of live microorganisms has a long history. Mention of cultured dairy products is found in the Bible and the sacred books of Hinduism. Soured milks and cultured dairy products, such as kefir, koumiss, leben and dahi, were often used therapeutically before the existence of microorganisms was recognized. The use of microorganisms in food fermentation is one of the oldest methods for producing and preserving food. Much of the world depends upon various fermented foods that are staples in the diet.

Élie Metchnikoff, the father of modern immunology, spoke highly about the possible health benefits of the lactic acid-bacteria (LAB) *Lactobacillus bulgaricus* and *Streptococcus thermophilus* in his writings at the turn of the last century. He wrote in his book, *The Prolongation of Life,* that consumption of live bacteria, such as *Lactobacillus bulgaricus* and *Streptococcus thermophilus,* in the form of yogurt was beneficial for gastrointestinal health, as well as for health in general, and for longevity. Some recent research suggests that certain live microorganisms may have immunomodulatory and anticarcinogenic effects, as well as other health benefits. There is presently much active research focusing on the development of target-specific probiotics containing well-characterized bacteria that are selected for their health-enhancing characteristics. These new probiotics are entering the marketplace in the form of nutritional supplements and functional foods, such as yogurt functional food products.

The gastrointestinal tract represents a complex ecosystem in which a delicate balance exists between the intestinal microflora and the host. The microflora are principally comprised of facultative anaerobes and obligate anaerobes. Approximately 95% of the intestinal bacterial population in humans is comprised of obligate anaerobes, including *Bifidobacterium, Clostridium, Eubacterium, Fusobacterium, Peptococcus, Peptostreptococcus* and *Bacteroides*. Approximately 1% to 10% of the intestinal population is comprised of facultative anaerobes, including *Lactobacillus, Escherichia coli, Klebsiella, Streptococcus, Staphylococcus* and *Bacillus*. Aerobic organisms are not present in the intestinal tract of healthy individuals with the exception of *Pseudomonas*, which is present in very small amounts. Most of the bacteria are present in the colon where the bacterial concentration ranges between 10^{11} to 10^{12} colony-forming units (CPU) per milliliter.

The intestinal microflora are important for maturation of the immune system, the development of normal intestinal morphology and in order to maintain a chronic and immunologically balanced inflammatory response. The microflora reinforce the barrier

function of the intestinal mucosa, helping in the prevention of the attachment of pathogenic microorganisms and the entry of allergens. Some members of the microflora may contribute to the body's requirements for certain vitamins, including biotin, pantothenic acid and vitamin B_{12}. Alteration of the microbial flora of the intestine, such as may occur with antibiotic use, disease and aging, can negatively affect its beneficial role.

The probiotics that are marketed as nutritional supplements and in functional foods, such as yogurts, are principally the *Bifidobacterium* species and the *Lactobacillus* species. Probiotics are sometimes called colonic foods. Most of the presently available probiotics are bacteria. *Saccharomyces boulardii* is an example of a probiotic yeast.

The following describe the various bacteria and yeasts used as probiotics:

BIFIDOBACTERIUM

Bifidobacteria are normal inhabitants of the human and animal colon. Newborns, especially those that are breast-fed, are colonized with bifidobacteria within days after birth. Bifidobacteria were first isolated from the feces of breast-fed infants. The population of these bacteria in the colon appears to be relatively stable until advanced age when it appears to decline. The bifidobacteria population is influenced by a number of factors, including diet, antibiotics and stress. Bifidobacteria are gram-positive anaerobes. They are non-motile, non-spore forming and catalase-negative. They have various shapes, including short, curved rods, club-shaped rods and bifurcated Y-shaped rods. Their name is derived from the observation that they often exist in a Y-shaped or bifid form. The guanine and cytosine content of their DNA is between 54 mol% and 67mol%. They are saccharolytic organisms that produce acetic and lactic acids without generation of CO_2, except during degradation of gluconate. They are also classified as lactic acid bacteria (LAB). To date, 30 species of bifidobacteria have been isolated. Bifidobacteria used as probiotics include *Bifidobacterium adolescentis, Bifidobacterium bifidum, Bifidobacterium animalis, Bifidobacterium thermophilum, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis* and *Bifidobacterium lactis*. Specific strains of bifidobacteria used as probiotics include *Bifidobacterium breve* strain Yakult, *Bifidobacterium breve* RO70, *Bifidobacterium lactis* Bb12, *Bifidobacterium longum* RO23, *Bifidobacterium bifidum* RO71, *Bifidobacterium infantis* RO33, *Bifidobacterium longum* BB536 and *Bifidobacterium longum* SBT-2928.

LACTOBACILLUS

Lactobacilli are normal inhabitants of the human intestine and vagina. Lactobacilli are gram-positive facultative anaerobes. They are non-spore forming and non-flagellated rod or coccobacilli. The guanine and cytosine content of their DNA is between 32 mol% and 51 mol%. They are either aerotolerant or anaerobic and strictly fermentative. In the homofermentative case, glucose is fermented predominantly to lactic acid. Lactobacilli are also classified as lactic acid bacteria (LAB). To date, 56 species of the genus *Lactobacillus* have been identified. Lactobacilli used as probiotics include *Lactobacillus acidophilus, Lactobacillus brevis, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus cellobiosus, Lactobacillus crispatus, Lactobacillus curvatus, Lactobacillus fermentum, Lactobacillus* GG *(Lactobacillus rhamnosus* or *Lactobacillus casei* subspecies *rhamnosus), Lactobacillus gasseri, Lactobacillus johnsonii, Lactobacillus plantarum* and *Lactobacillus salivarus. Lactobacillus plantarum* 299v strain originates from sour dough. *Lactobacillus plantarum* itself is of human origin. Other probiotic strains of *Lactobacillus* are *Lactobacillus acidophilus* BG2FO4, *Lactobacillus acidophilus* INT-9, *Lactobacillus plantarum* ST31, *Lactobacillus reuteri, Lactobacillus johnsonii* LA1, *Lactobacillus acidophilus* NCFB 1748, *Lactobacillus casei Shirota, Lactobacillus acidophilus* NCFM, *Lactobacillus acidophilus* DDS-1, *Lactobacillus delbrueckii* subspecies *delbrueckii*, *Lactobacillus delbrueckii* subspecies *bulgaricus* type 2038, *Lactobacillus acidophilus* SBT-2062, *Lactobacillus brevis, Lactobacillus salivarius* UCC 118 and *Lactobacillus paracasei* subsp *paracasei* F19.

LACTOCOCCUS

Lactococci are gram-positive facultative anaerobes. They are also classified as lactic acid bacteria (LAB). *Lactococcus lactis* (formerly known as *Streptococcus lactis*) is found in dairy products and is commonly responsible for the souring of milk. Lactococci that are used or are being developed as probiotics include *Lactococcus lactis, Lactococcus lactis* subspecies *cremoris (Streptococcus cremoris), Lactococcus lactis* subspecies *lactis* NCDO 712, *Lactococcus lactis* subspecies *lactis* NIAI 527, *Lactococcus lactis* subspecies *lactis* NIAI 1061, *Lactococcus lactis* subspecies *lactis* biovar diacetylactis NIAI 8 W and *Lactococcus lactis* subspecies *lactis* biovar diacetylactis ATCC 13675.

SACCHAROMYCES

Saccharomyces belongs to the yeast family. The principal probiotic yeast is *Saccharomyces boulardii. Saccharomyces boulardii* is also known as *Saccharomyces cerevisiae* Hansen CBS 5296 and *S. boulardii. S. boulardii* is normally a nonpathogenic yeast. *S. boulardii* has been used to treat diarrhea associated with antibiotic use.

STREPTOCOCCUS THERMOPHILUS

Streptococcus thermophilus is a gram-positive facultative anaerobe. It is a cytochrome-, oxidase- and catalase-negative organism that is nonmotile, non-spore forming and homofermentative. *Streptococcus thermophilus* is an alpha-hemolytic species of the *viridans* group. It is also classified as a lactic acid bacteria (LAB). *Steptococcus thermophilus* is found in milk and milk products. It is a probiotic and used in the production of yogurt. *Streptococcus salivarus* subspecies *thermophilus* type 1131 is another probiotic strain.

ENTEROCOCCUS

Enterococci are gram-positive, facultative anaerobic cocci of the Streptococcaceae family. They are spherical to ovoid and occur in pairs or short chains. Enterococci are catalase-negative, non-spore forming and usually nonmotile. Enterococci are part of the intestinal microflora of humans and animals. *Enterococcus faecium* SF68 is a probiotic strain that has been used in the management of diarrheal illnesses.

ACTIONS AND PHARMACOLOGY

ACTIONS

Probiotics may have antimicrobial, immunomodulatory, anticarcinogenic, antidiarrheal, antiallergenic and antioxidant activities.

MECHANISM OF ACTION

Lactobacillus plantarum 299v, which is derived from sour dough and which is used to ferment sauerkraut and salami, has been demonstrated to improve the recovery of patients with enteric bacterial infections. This bacterium adheres to reinforce the barrier function of the intestinal mucosa, thus preventing the attachment of the pathogenic bacteria to the intestinal wall. *Bifidobacterium breve* was found to eradicate *Campylobacter jejuni* from the stools of children with enteritis, although less rapidly than in those treated with erythromycin. *Lactobacillus* GG was found to eradicate *Clostridium difficile* in patients with relapsing colitis, and supplementation of infant formula milk with *Bifidobacterium bifidum* and *Streptococcus thermophilus* reduced rotavirus shedding and episodes of diarrhea in hospitalized children.

The antimicrobial activity of probiotics is thought to be accounted for, in large part, by their ability to colonize the colon and reinforce the barrier function of the intestinal mucosa. Probiotics, such as *Lactobacillus bulgaricus,* which do not adhere as well to the intestinal

mucosa, are much less effective against enteric pathogens. In addition, some probiotics have been found to secrete antimicrobial substances. These substances are known as bacteriocins. Such a bacteriocin has been isolated from *Lactobacillus plantarum* ST31, a probiotic derived from sour dough. The substance was found to be a 20 amino acid peptide. A different bacteriocin was isolated from another strain of *Lactobacillus plantarum*. The bacteriocin has 27 amino acids and contains lanthionine residues. This type of bacteriocin is classified as a lantibiotic.

Lactobacillus casei has been demonstrated to increase levels of circulating immunoglobulin A (IgA) in infants infected with rotavirus. This has been found to be correlated with shortened duration of rotavirus-induced diarrhea. *Lactobacillus* GG has also been shown to potentiate intestinal immune response to rotavirus infection in children. *Lactobacillus acidophilus* and *Bifidobacterium bifidum* appear to enhance the nonspecific immune phagocytic activity of circulating blood granulocytes. This effect may account, in part, for the stimulation of IgA responses in infants infected with rotavirus. In healthy individuals, *Lactobacillus salivarius* UCC118 and *Lactobacillus johnsonii* LA1 were demonstrated to produce an increase in the phagocytic activity of peripheral blood monocytes and granulocytes. Also, *Lactobacillus johnsonii* LA1, but not *Lactobacillus salivarius* UCC118, was found to increase the frequency of interferon-gamma-producing peripheral blood monocytes.

Lactobacillus GG has been shown to inhibit chemically induced intestinal tumors in rats. The probiotic appears to alter the initiation and/or promotional events of the chemically-induced tumors. *Lactobacillus* GG also binds to some chemical carcinogens.

Saccharomyces boulardii has been shown to prevent antibiotic-associated diarrhea and also to prevent diarrhea in critically ill tube-fed patients. The mechanism of this antidiarrheal effect is not well understood. *S. boulardii* has been found to secrete a protease which digests two protein exotoxins, toxin A and toxin B, which appear to mediate diarrhea and colitis caused by *Clostridium difficile*. The protective effects of *S. boulardii* on *C. difficile*-induced inflammatory diarrhea may, in part, be due to proteolytic digestion of toxin A and toxin B by a secreted protease.

Dietary antigens may induce an immunoinflammatory response that impairs the barrier function of the intestine, resulting in aberrant absorption of intralumenal antigens. This may account, in part, for food allergies. Probiotics that colonize the colon may be helpful in the management of some with food allergies by reinforcing the barrier function of the intestinal mucosa. *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 were found to produce significant improvement of atopic eczema in children with food allergies. The decrease in the signs and symptoms of atopic eczema occurred in parallel with a reduction in the concentration of circulating CD4+ T lymphocytes and an increase in transforming growth factor beta1 (TGF-beta1), indicating suppressive effects on T cell functions in this disorder. These probiotics may help restore the Th1/Th2 balance in atopic eczema.

Lactobacillus GG was found to scavenge superoxide anion radicals, inhibit lipid peroxidation and chelate iron *in vitro*. The iron chelating active of *Lactobacillus* GG may account, in part, for its antioxidant activity. Other lactic acid bacteria, including strains of *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Bifidobaterium longum* and *Streptococcus thermophilus*, have also demonstrated antioxidative ability. Mechanisms include chelation of metal ions (iron, copper), scavenging of reactive oxygen species and reducing activity.

PHARMACOKINETICS

The effectiveness of probiotics is related to their ability to survive in the acidic stomach environment and the alkaline conditions in the duodenum, as well as their ability to adhere to the intestinal mucosa of the colon and to colonize the colon. Some probiotics, such as *Lactobacillus* GG and *Lactobacillus plantarum* 299v, are better able to colonize the colon than others. After passage through the stomach and the small intestine, those probiotics that do survive become established transiently in the colon.

INDICATIONS AND USAGE

Probiotics have been used with some benefit in the prevention and treatment of some gastrointestinal disorders, including antibiotic-associated diarrhea and some infectious and viral diarrheas, most notably rotavirus-induced diarrhea in infants and children, lactose intolerance, sucrase and maltase deficiencies and inflammatory bowel disease. Probiotics may be of benefit in some with food allergies, but supporting evidence is preliminary. They may favorably modulate immunity in some circumstances and may have anticarcinogenic effects. There is the suggestion in some preliminary research that they may have some hypocholesterolemic activity. There is some evidence to support the use of probiotics to re-colonize the vaginas of women with recurrent vaginosis.

RESEARCH SUMMARY

Among the probiotics, only *S. boulardii, E. faecium* and *Lactobacillus sp*. have been useful in preventing antibiotic-related diarrhea. In one double-blind study, 180 hospitalized patients on antibiotic therapy were randomized to receive placebo or *S. boulardii* supplementation. Incidence of diarrhea was significantly lower among those receiving the probiotic, compared with controls (9% and 22%, respectively). These results have been confirmed in other controlled studies.

Lactobacillus GG significantly reduced the severity and duration of rotavirus diarrhea in infants in a double-blind, placebo-controlled study. Other researchers have demonstrated that the incidence of acute diarrhea and rotavirus shedding can be significantly reduced among infants admitted to the hospital by adding *Bifidobacterium bifidum* and *Streptococcus thermophilus* to infant formula. *Lactobacillus* GG has been shown helpful in the treatment of diarrhea associated with relapsing colitis due to *Clostridium difficile*. These studies, however, were small and uncontrolled. In a double-blind, placebo-controlled trial, *Saccharomyces boulardii* was significantly superior to placebo in treating diarrhea despite having no apparent effect on *Clostridium difficile* toxin. The use of probiotics in the attempted prevention and treatment of traveler's diarrhea, most commonly caused by enterotoxigenic *E. coli*, has produced inconclusive results. More study is needed.

Reduced fecal concentrations of various probiotics have been noted, although without conclusive power, in some with active ulcerative colitis, Crohn's disease, active pouchitis and some other inflammatory gastrointestinal conditions. *Lactobacillus* species prevented development of spontaneous colitis in interleukin 10-deficient mice. *Lactobacillus plantarum* ameliorated colitis that was already established in the same animal model.

In a clinical trial, subjects with chronic relapsing pouchitis given a probiotic preparation for nine months, consisting of *L. casei, L. plantarum, L. acidophilus* and *L. delbruekii* subspecies *bulgaricus*, had significantly fewer relapses than did unsupplemented subjects receiving placebo. No side effects were seen. Some researchers believe that *Lactobacillus* GG may also be useful in treating pouchitis.

Some lactic acid bacteria, including *L. plantarum, L. rhamnosus, L. casei* and *Lactobacillus bulgaricus,* have demonstrated immuno-regulatory effects that might help protect against some allergic disorders. There is some evidence that some of these probiotic strains can reduce the intestinal inflammation associated with some food allergies, including cow's milk allergy among neonates. Breast-fed infants of nursing mothers given *Lactobacillus* GG had significantly improved atopic dermatitis, compared with infants not exposed to this probiotic.

There are *in vitro*, animal and some preliminary human data suggesting that some probiotics can bind and inactivate some carcinogens, can directly inhibit the growth of some tumors and can inhibit bacteria that may convert precarcinogens into carcinogens. *L. acidophilus* and *L. casei* have exhibited the latter activity in human volunteers. There is some preliminary evidence that *L. casei* may have reduced the recurrence of bladder tumors in humans. Confirmatory trials are needed. Animal work has suggested that some

lactic-acid bacteria might help protect against colon cancer. Again, more research is needed.

Dairy products containing *L. acidophilus* have been credited with lowering cholesterol levels in some animal experiments. It has been hypothesized that bacterial assimilation of cholesterol in the intestine might reduce cholesterol stores available for absorption into the blood. To date, there is no credible evidence showing that any of the probiotics can lower cholesterol levels in humans. More study may be warranted. Yogurt has been used for some time as an "alternative" treatment for vaginitis. In an early test of this hypothesis, women with recurrent candidal vaginitis were treated with yogurt for six months. This was a crossover trial with subjects serving as their own controls. Daily ingestion of 8 ounces of yogurt significantly decreased both candidal colonization and infection.

Recently *L. acidophilus, L. crispatus and L. delbrueckii* subspecies *delbrueckii* all inhibited bacterial vaginosis-associated bacterial species *in vitro.* The researchers concluded that these probiotics might be useful for vaginal recolonization in women with recurrent vaginosis.

Owing to the fact that yogurt and some other probiotic-containing products are foods, rather than regulated pharmaceuticals, and owing to the fact that the probiotic content and potential of these food products may be highly variable, some researchers and clinicians have questioned the use of these products to treat vaginitis. In any event, larger better controlled studies are needed to further evaluate their reliability and efficacy in this context.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Probiotics are contraindicated in those hypersensitive to any component of a probiotic-containing product.

PRECAUTIONS

Pregnant women and nursing mothers should only use probiotic nutritional supplements if recommended by their physicians.

The use of probiotics for the treatment of any disorder must be medically supervised.

ADVERSE REACTIONS

The most common adverse reactions with use of probiotics are gastrointestinal and include flatulence and constipation. Probiotics are generally well tolerated.

Four cases of *Saccharomyces boulardii* fungemia have been reported. All of the patients had indwelling catheters, and the fungemia was thought to be due to catheter contamination.

There are a few reports of *Lactobacillus* bacteremia and endocarditis. In all cases, there were underlying conditions, including cancer, diabetes mellitus and recent surgery. There is one death reported secondary to *Lactobacillus* bacteremia.

There is one report of meningitis caused by *Bifidobacterium* in an infant.

INTERACTIONS

NUTRITIONAL SUPPLEMENTS

Prebiotics: Concomitant use of prebiotics and probiotics may enhance the effectiveness of the probiotics. See Prebiotics. See Symbiotics.

DOSAGE AND ADMINISTRATION

There are many probiotic products available. These products contain various *Lactobacillus* strains, various *Bifidobacterium* strains, combinations of lactobacilli and bifidobacteria and combinations of probiotics and prebiotics. Typical doses of probiotics range from one to ten billion colony-forming units (CFU) a few times a week. Probiotics need to be consumed at least a few times a week to maintain their effect on the intestinal microecology.

The development of probiotic-containing yogurt products is actively being pursued by major food companies. These yogurt products are functional yogurt food products.

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